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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/516,079 | 11/02/2005 | Vernon L Alvarez | 051530-5006-US | 2000 |

9629 7590 01/24/2007

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| EXAMINER | |
|---|---|
| CHISM, BILLY D | |
| ART UNIT | PAPER NUMBER |
| 1654 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
|---|---|---|
| 3 MONTHS | 01/24/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/516,079 | ALVAREZ ET AL. | |
| | Examiner | Art Unit | |
| | B. Dell Chism | 1654 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) 1-17 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-17 is/are rejected.

7)☒ Claim(s) 4 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 11/02/05.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

This is the first office action on the merits with claims 1-17 pending and under consideration.

### *Specification*

1. The use of trademarks has been noted in this application, for examples at pages 24-25 ADRIAMYCIN, TAXOL, and GEMZAR. For the use of any trademark in this specification, the trademark(s) should be capitalized wherever it/they appear(s) and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks.

2. The first paragraph of the Specification lists "Related Applications", however, no reference was made to the international application. Applicant is asked to amend this paragraph to include reference to the international application from which the instant application is a national stage entry.

### *Claim Objections*

3. Claim 4 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 1. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). See Indefinite rejection below for reasoning on this objection.

***Claim Rejections - 35 USC § 112***

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claims 1-3 are rejected as indefinite because it is unclear as to the meaning of the phrase "in combination" in claim 1. "In combination" carriers the interpretation of "together"; however, claims 2-3 appear to redefine "in combination" by stating that one of the compounds can be administered at a totally different time and in reverse order. Based on this ambiguity, the claims are rejected for indefiniteness. Additionally, because claim 1 can be interpreted as the compounds administered together, then claim 4 is considered a duplicate claim of claim 1 (see Claim Objections above).

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is also referred to the Guidelines on Written Description published at FR 66(4) 1099-1111 (January 5, 2001) (also available at www.uspto.gov).

*Vas-Cath Inc. v. Mahurka*, 19 USPQ2d 1111, states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the "written description" inquiry, is *whatever is now claimed*" (see page 1117).

A review of the language of the claims indicates that these claims are drawn to a genus, i.e., chlorotoxin derivatives, and defined in the specification at page 11 to be synonymous with variant.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In *Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that, while applicants are not required to disclose every species encompassed by a genus, the description of the genus is achieved by the recitation of a representative number of species falling within the scope of the claimed genus. At section B(1), the court states "An adequate written description of a DNA ... requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention".

There is language in the specification at pages 11-12 defining derivatives of chlorotoxin comprising SEQ ID NOs: 8 and 13 that are within the scope of the claimed genus. The disclosure of a small representative number of the species of the genus may provide an adequate written description of a genus when the species disclosed are representative of the genus. However, the present claims encompass numerous species that are not so described, because there is

substantial variability among the species. The language of the specification allows for multiple deletions and multiple insertions, which can be either conservative or non-conservative, wherein the modifications can have a range of affects on the functionality of the disclosed invention. The specification allows for modifications as described above that enhance, neutralize or inhibit characteristics of the claimed invention. One cannot clearly envisage the full breadth of the claimed genus and would not consider the Applicants in possession of claimed invention at the time of filing.

One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genus of which comprises all chlorotoxin derivatives as defined broadly. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (see *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

9. Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treating and detecting human glioblastoma multiforme, human malignant melanoma, human prostate tumor and human small cell lung carcinoma does not reasonably provide enablement for all other cancers as instantly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2d 1400 (Fed. Cir., 1988) as to undue

experimentation. Each factor is addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation. The factors follow:

**1-2. the nature of the invention and the breadth of the claims**; the terms of the claims indicates that the instant invention is applicable to treatment and/or detection of the presence of all cancer, to include all human and non-human animals. This would include all cancer regardless of the lack of mode of cell proliferation and growth, and would include treatment of and/or detection of all cancer regardless of the ability of the instant invention to inhibit/kill the neoplasm/tumor. There are no metes and bounds to the cancer to be treated and /or detected and there are no metes and bounds to the patient classes for which the cancer can be treated and /or detected using the instantly claimed inventions.

**3. the predictability or unpredictability of the art**; the prior are indicates that the chlorotoxin targets the chloride ion channel of glioma cells; however, the exact antigen targeted by chlorotoxin has not been unequivocally identified (see US 6,667,156 B2 column 10 lines 40-49). Therefore, with the lack of understanding in the prior for the use of the instantly claimed compounds in regards to targeting cancers based on the ability of chlorotoxin to target this chloride ion channel, it would be highly unpredictable to apply the instant invention to all other forms of cancer and patient classes without an understanding of the mechanism upon which the chlorotoxin would act/react.

**4. the amount of direction or guidance presented**; other than in vitro and xenograft studies for methods of treating and detecting human glioblastoma multiforme, human malignant melanoma, human prostate tumor and human small cell lung carcinoma, the

specification is lacking direction or guidance that would indicate the instantly claimed invention would invariably work for treating and detecting all other cancers in all other possible patient classes. There is no particular nexus that would lead one to see the mechanism by which the chlorotoxin (CTX) would necessarily demonstrate efficacious characteristics for treating and/or detecting all other cancers because not all cancers demonstrate that aspect upon which the CTX acts/reacts. Soroceanu et al. (Cancer Research, November 1, 1998, Vol. 58, pages 4871-4879) teaches that CTX focuses on the chloride ion channel (GCC) of gliomas of brain tumors. Conversely, the instant application does not establish a nexus between the enabled cancers, i.e., human glioblastoma multiforme, human malignant melanoma, human prostate tumor and human small cell lung carcinoma, and the properties of all other cancers in all other animals including humans. The specification is lacking in guidance as how to avoid pitfalls/inconsistencies in applying the present invention to all other cancers in all animals other than those instantly enabled for.

**5. the presence or absence of working examples**; based on the lack of direction and or guidance in the specification for the treating and/or detection of all cancers in all patient classes, the specification would require presented data that might be extrapolated/interpreted/assessed that would at least indicate expectation of success in all other cancers and patient classes. However, the instant specification is lacking in working examples that would, in light of a demonstrated mechanism common to all other cancers and patient classes, be example enough to apply to all other cancers.

**6. the quantity of experimentation necessary**; Given the lack of predictability given the knowledge in the prior art, and given the lack of direction and guidance in the specification for extrapolating data to cover all other cancers and patient classes, and given the lack of working examples in the specification allowing for reasonable assessment of the expansion of the instantly enabled for cancers, there would be an undue burden of experimentation requiring further studies to elicit the mechanisms of all other cancers in all other patient classes to establish the nexus that would allow for treatment and/or identification of all other cancers in all other patient classes.

**7. the state of the prior art**; The state of the art in treating cancer in humans is unpredictable, as stated by Dr. Richard Klausner (C Gorman, et al. The Hype and the Hope. Time (1998) 151(19) pages 40-44. Included HTML copy referenced pages 1-9), "We have cured mice of cancer for decades - and it simply didn't work in people." (Page 1) Further, the state of the art with angiogenesis inhibitors is unpredictable, as stated in the same article, "Nor will angiogenesis inhibitors work equally well against all cancers." (Page 3).

Additionally, with regards to *in vivo* models, Gura (T Gura. Systems for Identifying New Drugs are Often Faulty. Science (1997) 278 (7 Nov) 1041-1042) states, "Pharmaceutical companies often test drug candidates in animals carrying transplanted human tumors, a model called a xenograft. But not only have very few of the drugs that showed anticancer activity in xenografts made it into the clinic, a recent study...suggests that the xenograft model missed effective drugs. The animals apparently do not handle the drugs exactly the way the human body does," (Page 1041) and with regards to xenograft

models, "tumors don't behave like naturally occurring tumors in humans - they don't spread to other tissues, for example. Thus, drugs tested in the xenografts appeared effective but worked poorly in humans." (Page 1041). Further it is stated that they, "had basically discovered compounds that were good mouse drugs rather than good human drugs" (Page 1041).

With regards to *in vitro* models, Dermer (GB Dermer. Another Anniversary for the War on Cancer. Bio/Technology (1994) 12(Mar) page 320) teaches that the model systems cell lines for cancer are "unsuitable for the job". He states that the "Petri dish cancer is a really poor representation of malignancy, with characteristics profoundly different from the human disease."

Further, with regards to *in vitro* models, McKie (R McKie. Cancer Research Set Back a Decade. The Observer (2001) (10 June) pages 1-4 (HTML text).) states that, "Hundreds of cancer research projects have produced worthless or misleading results because the scientists have been using incorrectly identified samples." (Page 1), estimated to be, "up to 1/3 of the cell lines" (Page 2), and that, "Hundreds of research papers on these cell lines have already been published, however, and most of their conclusions are invalid, say experts." (Page 3).

Alan Oliff states in Gura that, "[t]he fundamental problem in drug discovery for cancer is that the model systems are not predictive at all." (Page 1041). Since the models systems are highly unpredictable for treating cancer and determining effective compounds remains largely unsolved, means for treating, curing, or preventing all cancer and

preparing an 'effective amount' (dose) of the compositions for treating, curing, or preventing all cancer is highly unpredictable.

Although the instant invention is enabled for methods of treating and detecting human glioblastoma multiforme, human malignant melanoma, human prostate tumor and human small cell lung carcinoma, the specification does not compensate for the deficiencies in the prior art in regards to treatment of all cancers in all patient classes. The examiner is not challenging the xenograft studies as presented for human glioblastoma multiforme, human malignant melanoma, human prostate tumor and human small cell lung carcinoma; however, there simply is a lack of support for the extrapolation of that data to all other forms of cancer in all other patient classes.

**8. the relative skill of those skilled in the art**; In view of the discussion of each of the preceding seven factors the level of skill in this art is high and is at least that of a medical doctor or Ph.D with several years of experience in the art. As the cited art would point to, even with a level of skill in the art predictability of the results is not invariable.

In consideration of each of factors 1 - 8, it is apparent that there is undue experimentation because of variability in prediction of outcome that is not addressed by the present application disclosure, examples, teaching, and guidance presented. Absent factual data to the contrary, the amount and level of experimentation needed is undue.

### *Claim Rejections - 35 USC § 102*

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claims 14-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Soroceanu et al. (Cancer Research, November 1, 1998, Vol. 58, pages 4871-4879). Soroceanu et al. teaches the use of chlorotoxin (CTX) for targeting tumors with radiolabeled CTX, for example labeling with $^{125}I$ and $^{131}I$. The compounds were used to target brain tumors.

12. Claims 14-17 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent No. 6,667,156 B2 ('156). '156 teaches the use of chlorotoxin (CTX) for targeting tumors with radiolabeled CTX, for example labeling with 3H, 14C, 32P, 35S, 36CL, 51CR, 57Co, 59Fe, 90Y, 186Re, $^{125}I$, and $^{131}I$. The compounds were used to target brain tumors, gliomas, meningiomas, ependymonas, medulloblastomas, neuroblastomas, glioblastomas, gangliomas, pheochromocytoma, melanoma, sarcoma, small cell lung carcinoma and metastitic brain tumors.

### *Claim Rejections - 35 USC § 103*

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 1-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pre-Grant Publication No. 2002/0146749 ('6749) in combination with US Pre-Grant Publication 2001/0055751 A1 ('5751).

'6749 teaches the use of chlorotoxin (CTX) for targeting tumors with radiolabeled CTX, for example labeling with 3H, 14C, 32P, 35S, 36CL, 51CR, 57Co, 59Fe, 90Y, 186Re, $^{125}$I, and $^{131}$I. The compounds were used to target brain tumors, gliomas, meningiomas, ependymonas, medulloblastomas, neuroblastomas, glioblastomas, gangliomas, pheochromocytoma, melanoma, sarcoma, small cell lung carcinoma and metastitic brain tumors. Additionally, '6749 teaches compositions and treatment of the cancers comprising administration of chlorotoxin (CTX) in combination with cytotoxic moieties of gelonin, ricin, saponin, pseudonomas exotoxin, pokeweed antiviral protein, and diphtheria toxin. Conversely, '6749 does not teach those chemotherapeutic agents as instantly claimed.

'5751 teaches prostate carcinoma treatments comprising the use of immunoconjugates with cytotoxic agents such as ricin, doxorubicin, daunorubicin, mitomycin, etoposide,

tenoposide, vincristine, vinblastine, diphtheria toxin, pseudomonas exotoxin, and gelonin, for examples. Conversely, '5751 does not teach the use of chlorotoxin in the compositions or their uses.

'5751 corrects the deficiencies of the '6749 reference by showing that it would be obvious to one of ordinary skill in the art to substitute and/or utilize in combination those cytoxic compounds of '6749 with those cytotoxic compounds of '5751, because the '5751 teaches that the genus of compounds serve clearly in the prior art as exchangeable or substitutable components in the cancer arts for the purposes of serving as chemotherapeutic agents. One of ordinary skill in the art would be motivated by the combined teachings of '6749 and '5751, because '6749 is drawn to the same cancer genus as is presently offered by using the CTX in combination with a cytotoxic/chemotherapeutic agent as defined in '6749. Furthermore, one of skill in the art would be motivated to use, in combination or as substitute, those cytotoxic/chemotherapeutic agents as taught in '5751 wherein the components are known in the prior art to be interchangeable or for use together in anti-cancer compositions and uses thereof. Therefore, it would have been obvious to combine the cytotoxic/chemotherapeutic agents taught in overlap by the two references for the genus of cancers taught in the two references that are instantly claimed, and one of ordinary skill in the art would have a high expectation of success in using those obvious compounds for treatment of those cancers.

***Conclusion***

16. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to B. Dell Chism, whose telephone number is (571) 272-0962. The examiner

can normally be reached on M-F 08:30 AM - 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562.

The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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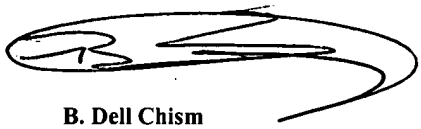

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